DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

M33201

December 22, 1999

CBER-00-009

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Thomas J. Novitsky, Ph.D.
President and CEO
Associates of Cape Cod, Inc.
704 Main Street
Falmouth, MA 02540

Dear Dr. Novitsky:

During our September 27 through October 8, 1999 inspection of your facility located at 704 Main Street, Falmouth, Massachusetts, our investigators documented violations of Section 501(h) of the Federal Food, Drug, and Cosmetic Act and Title 21, Code of Federal Regulations, (CFR), Subchapter F, Parts 600-680 and Subchapter H, Part 820, as follows:

1. Failure to establish and maintain procedures for the control of storage areas and stock rooms for product to prevent mix-ups, damage, deterioration, contamination, or other adverse effects pending use or distribution [21 CFR 820.150]. Inspection of the basement media fill incubation area and component and final storage areas found the presence of heavy mold contamination. Mold contamination in this area was included as a contributing factor in media fill failures, per Non-Conformance Report (NCR) dated 11/3/98.

2. Failure to verify or validate the corrective and preventive action(s) to ensure that such action is effective and does not adversely affect the finished device [21 CFR 820.100(a)(4)]. For example:

   a. the NCR dated 11/3/98 indicates that the ——— pallets in the basement used to store production materials and media fill samples should be replaced with plastic pallets to alleviate the presence of mold. As of 10/6/99, not all of the ——— pallets were replaced, and there was continuing evidence of mold in the basement.

b. the NCR dated 11/5/97 indicates that the [redacted] in the [redacted] lyophilizer [redacted] needs to be replaced to correct a freon leak. There is no indication that this correction was done.

c. the NCR dated 2/17/99 indicates that the [redacted] filler in room #2 needs adjustment to prevent crashing of the needles. There is no indication that this corrective action was taken.

3. Failure to implement and record changes in methods and procedures needed to correct and prevent identified quality problems [21 CFR 820.100(a)(5)]. For example:

a. the NCR dated 5/22/99 indicates that the [redacted] switch was incorrectly set on the [redacted] lyophylizer [redacted] There is no indication that corrective and preventive actions were taken.

b. the NCR dated 4/27/99 indicates that SOP #306 Rev 1 needs revision to reflect new specifications for [redacted] raw material. The Standard Operating Procedure (SOP) has not been revised and the [redacted] raw material continues to be tested and released using the unrevised SOP.

c. the NCR dated 10/23/97 indicates that [redacted] be used when making pH measurements and that this preventive action be included in the appropriate SOPs. The SOPs have not yet been corrected and the [redacted] is not being used.

4. Failure to establish and employ appropriate statistical methodology to detect recurring quality problems [21 CFR 820.100(a)(1)]. For example:

a. trending of identified quality issues is not conducted. There are no procedures for trending NCRs for corrective actions.

b. there are no procedures for applying outlier tests in evaluating out of specification test results. For example, the [redacted] test was used to discard results obtained during re-validation of the [redacted]

5. Failure to investigate the cause of nonconformities related to product, processes, and the quality system [21 CFR 820.100(a)(2)]. For example:

a. out of specification values are discarded without investigation. In calculating response characteristics for [redacted] and Pyrotell-T lot # 599-01-089T, vials that did not conform to specifications were not used in the calculations. Outliers were discarded and negative controls that showed activity were ignored.

b. investigations are not conducted for initial sterility tests that are out of specification.

6. Failure to establish, maintain, and follow procedures for process validation in order to ensure that processes have been adequately validated and that the specified requirements continue to be met [21 CFR 820.75]. For example:

   a. the cleaning procedure for the lyophilizers, described in SOP 114, has not been validated.

   b. the ——— test method performed on the ——— for product release has not been validated.

   c. the ——— lyophilization cycle changes for 5 ml vials, in January 1997, were not validated.

   d. the stopper wash/depyrogenation processing for autoclave ← has not been completely validated.

7. Failure to develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications [21 CFR 820.70(a)]. For example:

   a. media fills do not always represent the filling processes they are designed to simulate. For example in room #1, vials are filled in volumes of —— to —— but media fills for this room are always done in ——volumes.

   b. the media fill SOPs, 065-PQ and 069-PQ, do not require simulation of all interventions and processes of a normal filling. For example, media fills are not routinely ——— as is done with product.

   c. potency testing for lot release of Pyrotell-T and ——— are not being conducted per SOP #113, in that ——— is not performed.

   d. growth promotion testing is not performed in accordance with the license requirements. For example, growth promotion is not conducted using soybean casein digest medium.

   e. there are no provisions for the monitoring of lots of Limulus Amebocyte Lysate (LAL) products that are released after unusual processing conditions or test results.

   f. container closure integrity studies have not been performed for LAL products.

8. Failure to establish, maintain, and follow procedures to adequately control environmental conditions that could reasonably be expected to have an adverse effect on product quality [21 CFR 820.70(c)]. For example:

a. there is no validation data to support room classifications.

b. sampling frequency and sites for environmental monitoring in Bottle Room #1 have not been validated.

c. integrity testing is not performed for the HEPA filters in Bottle rooms 1 and 2.

9. Failure to ensure that all equipment used in the manufacturing process meets specified requirements and is appropriately designed, constructed, placed, and installed to facilitate maintenance, adjustment, cleaning, and use [21 CFR 820.70(g)]. For example:

a. there is no schedule for routine maintenance and re-validation for the — lyophilizers.

b. the — filters between the ——— and lyophilizers are not integrity tested.

c. there are no procedures for the maintenance of the dry heat ovens, and the —— filler in Bottle Room #2.

10. Failure to establish and maintain procedures to ensure that device history records for each batch, lot or unit are maintained to ensure that the device is manufactured in accordance with the device master record and the requirements of Part 820 (Quality System Regulation) [21 CFR 820.184] in that record review and approval practices do not identify data reporting and recording errors. For example:

a. sensitivity data for lots S98-054 and 598-07-074 contained erroneous data, which was reported to FDA as part of the package for lot release.

b. batch record form 077 erroneously recorded the — sensitivity observed in several CSE qualifying tests.

c. raw data was erroneously transferred to typed records for lot 250099C.

d. raw data was transferred erroneously to —— database when performing PQ for ——————————— This data was used for statistical and trending analysis

11. Failure to establish and maintain procedures to ensure that sampling methods are adequate for their intended use and are based on a valid statistical rationale [21 CFR 820.250(b)]. For example:

a. a complaint dated 4/8/98 indicates that a customer returned — vials of Pyrotell-T lot #597-10-037-T due to problems with slow times. The potency test for Pyrotell-T requires testing — vials ——— for mid-range curves and — vials —

for low range curves. Only out of the vials underwent potency testing and the remaining vials were returned to inventory.

b. a complaint dated 5/5/99 indicates that a customer returned vials of Multitest Pyrotell Gel-Clot Formulation lot #598-08-079 due to problems with sensitivity. The potency release test for Pyrotell multitest vials requires testing vials. Only out of vials underwent potency testing and the remaining vials were returned to inventory.

c. a complaint dated 6/9/99 indicates that a customer returned vials of Multitest Pyrotell lot #12-80-672 due to problems with sensitivity. The potency release test for Pyrotell multitest vials requires testing vials. Only out of vials underwent potency testing and the remaining vials were returned to inventory.

d. there is no assurance that sampling of the filling operations is representative of the lot being filled. For example, samples are taken only from the beginning and end of the run for products filled in Bottle Room # 1. There are no set limits on the number of fill check vials that can be discarded prior to invalidating a fill run.

12. Failure to retain a quantity of each lot of product sufficient for examination and testing for safety and potency [21 CFR 600.13].

13. Failure to review and evaluate all complaints to determine whether an investigation is necessary and to document the reason [21 CFR 820.198(b)] in that, for the period of time from March 1999 to October 1999, there were telephone correspondences with 8 different consignees attesting to potential problems with products which were not investigated as complaints.

14. Failure to establish and maintain procedures to ensure that complaints are evaluated to determine whether the complaint represents an event which is required to be reported to the FDA [21 CFR 820.198(a)].

15. Failure to inform FDA about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling, established in the approved license application [21 CFR 601.12]. For example, changes in the Pyrochrome buffer specifications were not reported to the FDA.

16. Failure to maintain specifications, test procedures, and work instructions as part of the Device Master Record [21 CFR 820.181]. For example:

a. when qualifying a Control Standard Endotoxin (CSE) for use with a turbidimetric test, there are no specifications as to the range of potencies that can be averaged to obtain the mean standard potency.

b. there are no established raw material specifications for

c. there are no written specifications for acceptance of microplates.

d. work instructions are not included in the Device Master Record.

17. Failure to establish and maintain procedures to prevent contamination of equipment or product by substances that could reasonably be expected to have an adverse effect on product quality [21 CFR 820.70(e)]. For example:

a. water testing specifications, procedures and practices do not assure that quality requirements are met. For example:

i. no microbial analysis is performed on product water from the ——— water system.

ii. an overflow pipe for the still line in the ———. water system is open to the atmosphere without sterile air filtration.

iii. a nonfunctional section of pipe off the condenser in the ——— water system is reconnected to a line that feeds the still.

b. endotoxin testing of the ——— water is not always performed ——— ——— as required by the SOP.

c. the ——— solution used to maintain pH meters is not assigned an expiration date nor replaced at regular intervals. The solution in use on 10/1/99 was uncovered and had a white residue around the opening of the bottle.

d. operators loading the lyophilizers were noted going back and forth between class ——— and class ——— areas.

18. Failure to evaluate and select potential suppliers, contractors, and consultants on the basis of their ability to meet specified requirements, including quality requirements, and to document the evaluation [21 CFR 820.50(a)] in that, vendor audits are not routinely conducted.

We acknowledge receipt of your written responses dated October 29, 1999; November 15, 1999; and December 1, 1999, to the Form FDA-483 issued at the close of the inspection. We have reviewed your responses and find that they are inadequate to address our concerns and we have the following specific comments to your responses, which are numbered to correspond to the observations listed on the Form FDA-483:

1a, 2a We acknowledge the corrective actions your firm has taken to control the mold contamination in your firm, however, we view these as only temporary measures. We would like to have a meeting with you to discuss our concerns about the high level of

mold contamination in your facility and potential permanent actions that may be necessary to prevent the problem in the future. We will contact you on potential dates and times for the meeting. The recommended meeting should not, however, delay your corrective action response to this letter within 15 working days, as noted below.

2. Please address the measures that will be taken to ensure that corrective and preventive actions will be fully investigated, implemented, and documented as is required under 21 CFR 820.100.

3. Please clarify whether validation studies to support room classifications have been conducted.

6. Please be aware that FDA must be informed of each change in the product, production process, quality controls, equipment, facilities, and labeling as required under 21 CFR 601.12.

16b. Please be aware that FDA must be informed of a change of specifications as required under 21 CFR 601.12.

16c. Please provide the specifications for the action limits.

17. Please be advised that 21 CFR 610.12 allows retest procedures but does not exempt the initial failures from investigations. The investigation of nonconformities relating to product, processes, and the quality system is required under 21 CFR 820.100.

Neither the above violations nor the observations noted on the Form FDA 483, presented to you at the conclusion of the inspection, are intended to be an all-inclusive list of deficiencies at your establishment. It is your responsibility to ensure adherence to each requirement of the Federal Food, Drug, and Cosmetic Act and the applicable regulations and standards. The specific violations noted in this letter and on the Form FDA 483 may be symptomatic of serious underlying problems in your establishment's manufacturing and quality systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems, you must promptly initiate permanent corrective actions.

You should take prompt action to correct these deviations. Failure to do so may result in regulatory action without further notice. Such action includes license suspension and/or revocation, seizure, injunction, and/or civil penalties. Federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts. In addition, no license applications or supplements for devices to which the deficiencies are reasonably related will be approved until the violations have been corrected.

You should respond to FDA in writing within 15 working days of receipt of this letter of the steps you have taken to correct the noted violations and to prevent their recurrence. If corrective

actions cannot be completed within 15 days, state the reason for the delay and the time within which the corrections will be completed. FDA will verify your implementation of the promised corrective actions during the next inspection of your facility.

Your reply should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448, Attention: Division of Case Management, HFM-610. If you have any questions regarding this letter, please contact Cathy Conn at (301) 827-6201.

Sincerely,

for Deborah Ralston
Director
Office of Regional Operations